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(57) Abstract

Novel sulphonamide derivatives having CNS activity, processes for their preparation and their use as medicaments.

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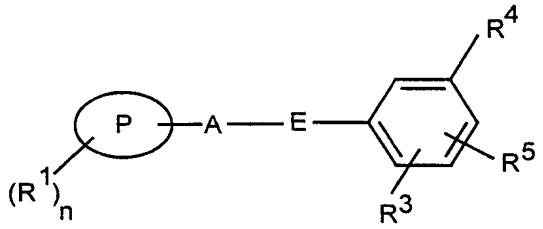
NOVEL COMPOUNDS

This invention relates to novel sulphonamide compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

US patent 5,703,072 discloses bicyclic nonane and decane compounds having dopamine receptor affinity which are claimed to be of use in the treatment of schizophrenia. US patent 5,457,121 discloses cis-hexahydro-5-(1,2,3,4-Tetrahydro-2-naphthalenyl)pyrrolo<3,4,c>pyrroles as inhibitors of serotonin reuptake. European patent application EP 0815861 discloses a series of aryl sulphonamide compounds that are said to possess 5-HT_6 receptor activity and are useful in the treatment of various CNS disorders. A structurally distinct class of compounds has now been discovered, which have been found to have 5-HT_6 receptor antagonist activity.

The present invention therefore provides, in a first aspect, a compound of formula (I) or a salt thereof:



(I)

in which

E is $-SO_2NH-$ or $-NHSO_2-$

P is a phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

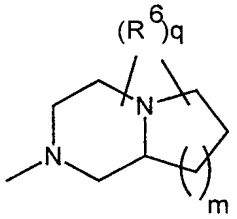
R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{1-6}alkoxy, OCF_3, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, amino, alkylamino or dialkylamino, SR^{11} where R^{11} is hydrogen or C_{1-6}alkyl or R^1 is phenyl, benzyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; and

n is 0, 1, 2, 3, 4 or 5;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$;

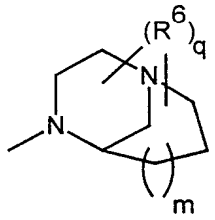
R^4 is selected from a group of formula (i), (ii) or (iii):

Formula (i)



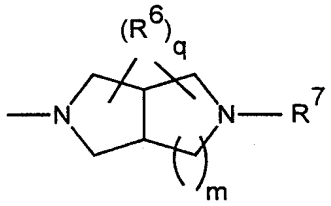
in which R^6 is C_{1-6}alkyl optionally substituted by one or more halogen atoms;
m is 0, 1 or 2;
q is 0, 1, 2, 3 or 4; or

Formula (ii)



in which R^6, m and q are as defined in formula (i); or

Formula (iii)



in which R^6, and q are as defined in formula (I) and R^7 is hydrogen or C_{1-6}alkyl;
R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy optionally substituted with one or more fluorine atoms, trifluoromethyl, or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

When the group P is a bicyclic heterocyclic ring suitable examples include benzothienyl, indolyl, quinolinyl or isoquinolinyl. When P is a 5 to 7-membered heterocyclic ring suitable examples include thienyl, furyl, pyrrolyl, triazolyl, diazolyl,

imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrrolidinyl and pyrazinyl. The heterocyclic rings can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen.

Preferably P is phenyl, naphthyl, thienyl and most preferably benzothienyl,

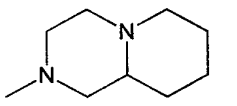
Suitably A is a single bond, a methylene or ethylene group or a -CH=CH- group. Preferably A is a single bond or methylene.

Suitably R^1 is hydrogen, halogen, phenyl, C_{1-6}alkoxy most preferably OMe, SR^{11} most preferably SMe or C_{1-6}alkyl optionally substituted by one or more fluorine atoms, for example methyl or trifluoromethyl. When R^1 is a heterocyclic group suitable examples include those listed above for P. Preferably n is 1, 2 or 3.

It will be appreciated that when R^3/R^5 groups are linked together the two groups must be attached to adjacent carbon atoms of the phenyl ring.

Preferably R^3 is a group R^5, in particular hydrogen.

Preferably R^4 is a group: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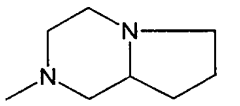
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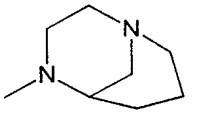
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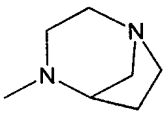
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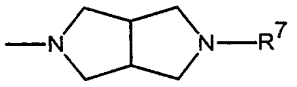
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Preferably R^5 is C_{1-6}alkoxy, most preferably methoxy. Preferably R^5 is para with respect to the sulphonamide linkage.

Particularly preferred compounds of the invention include
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[4-methoxy-3-(octahydropyrido[1,2-α]pyrazin-2-yl) phenyl] amide,
S-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2-α]pyrazine-2-yl)-4-methoxyphenyl],
R-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2-α]pyrazine-2-yl)-4-methoxyphenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[3-(1,4-diazabicyclo-[3.3.1]non-4-yl)-4-methoxyphenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(1,4-diazabicyclo-[3.2.1]oct-4-yl)-4-methoxyphenyl]amide,

5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [4-methoxy-3-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)phenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydropyrrolo-[3,4-*c*]pyrrol-2-yl)-4-methoxyphenyl]amide,
N-(5-Bromo-3-fluoro-2-methoxyphenyl)-4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-c]pyrrol-2-yl]-benzenesulfonamide,
and pharmaceutically acceptable salts thereof.

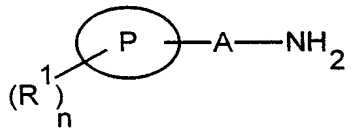
The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

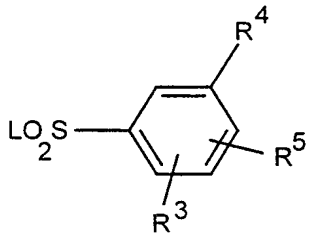
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) when E is a group $-NHSO_2^-$, the coupling of a compound of formula (II):



(II)

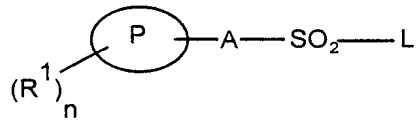
in which R^1, P, n and A or protected derivatives thereof with a compound of formula (III):



(III)

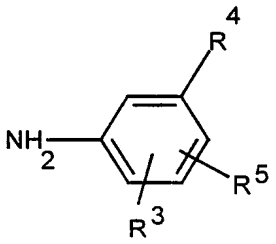
in which R^3, R^4 and R^5 are as defined in formula (I) and L is a leaving group; or

(b) when E is a group $-SO_2NH-$, the coupling of a compound of formula (IV):



(IV)

in which R^1, P, n and A are defined in formula (I) and L is a leaving group with a compound of formula (V) or protected derivatives thereof:



(V)

in which R^3, R^4 and R^5 are as defined for formula (I)
and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

Suitable leaving groups include halogen such as chloro or bromo, in particular chloro. The reactions of compounds of formula (II) and (III) and that of compounds of formula (IV) and (V) are typically carried out by mixing the two reagents together, optionally in an inert solvent such as dichloromethane or acetone. Such a reaction may be carried out in the presence of base.

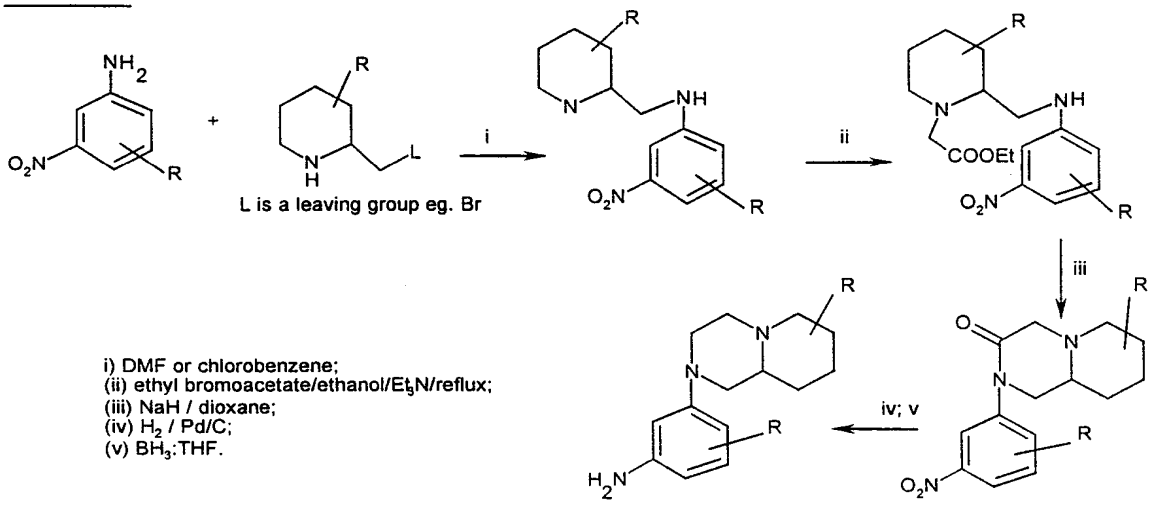
Those skilled in the art will appreciate that it may be necessary to protect certain groups. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981). For example, suitable protecting groups for the piperazine group include BOC, $COCCl_3$, $COCF_3$ and methyl the latter of which may be removed by treatment with 1-chloroethyl chloroformate according to standard procedures.

Compounds of formulae (II) to (IV) are commercially available or may be prepared according to known or analogous methods or following procedures described below. The procedures below are by way of illustration rather than limitation.

A compound of formula (III) (in which R^4 is a group of formula (iii)), that is, 4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-c]pyrrolo-2-yl)-benzenesulfonyl chloride can be prepared by coupling *cis*-hexahydro-2-methylpyrrolo[3,4-c]pyrrole hydrochloride (US 5,457,121) with 2-bromoanisole using a palladium coupling reaction according to the general methodology disclosed by Buchwald (Tet. Lett. **1997**, 38, 6359-6362). The resulting amine can be treated with chlorosulfonic acid in dichloromethane to give the required compound.

Aryl octahydropyrido[1,2-*a*]pyrazines of formula (V) (in which R^4 is a group of formula (i)), can be obtained by a synthetic procedure as represented by scheme 1.

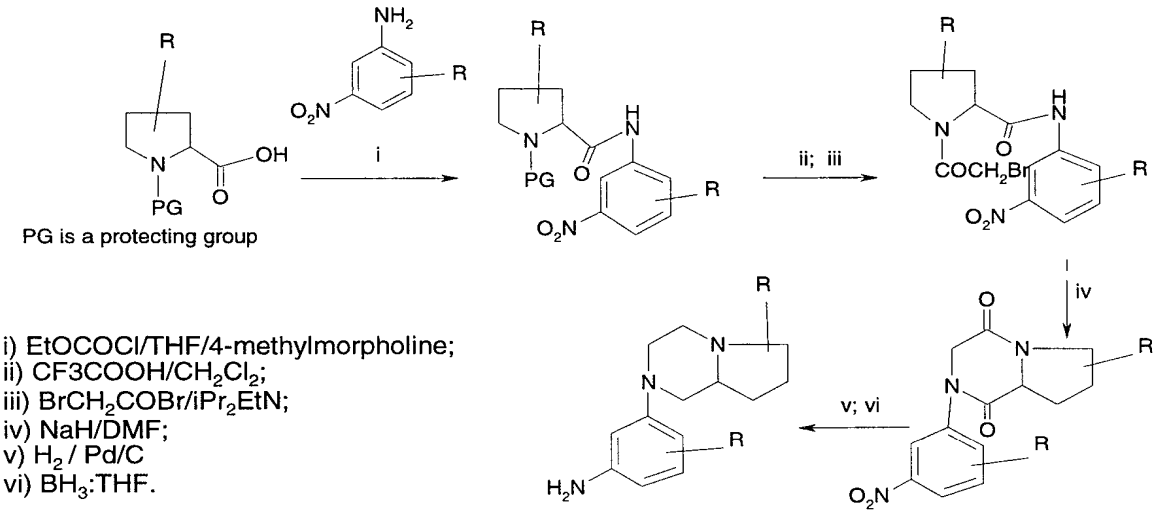
Scheme 1



Alternatively a modified strategy based on the use of a suitably protected proline derivatives can be used to prepare hexahydropyrrolo[1,2-a]pyrazines of general formula (V) using a synthetic procedure as represented by scheme 2. It is

noted that both enantiomers can be prepared starting from the appropriate chiral proline.

Scheme 2



Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_6$ receptor antagonist activity and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders e.g. Alzheimers disease, Parkinson' Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythym), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

(2-Methoxy-5-nitrophenyl)piperidin-2-ylmethylamine (D1)

A mixture of 2-bromomethylpiperidine hydrobromide[1] (3.0 g, 11.6 mmol) and 2-methoxy-5-nitroaniline (34.8 mmol, 5.85 g) in chlorobenzene (100 mL) was heated under reflux for 17 h. The solvent was removed and the residue was dissolved in dichloromethane (100 mL), washed with 10% aqueous sodium hydroxide (3 x 20 mL) and dried ($MgSO_4$). The solvent was removed and the residue was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (D1) as a dark green solid (1.45 g, 47%). MS: m/z (MH+) = 266.

1. T. A. Crabb and R. F. Newton, *Tetrahedron,* 1968, **24**, 2485.

Description 2

{2-[(2-Methoxy-5-nitrophenylamino)methyl]piperidin-1-yl}acetic acid ethyl ester (D2)

A mixture of (2-methoxy-5-nitrophenyl)piperidin-2-ylmethylamine (D1) (0.27 g, 1 mmol), ethyl bromoacetate (0.15 mL, 1.35 mmol) and triethylamine (0.19 mL, 1.35 mmol) in dry ethanol (20 mL) was heated under reflux for 4 hours. The solvent was removed, the residue was dissolved in dichloromethane (70 mL), washed with aqueous sodium hydrogen carbonate (2 x 10 mL) and dried ($MgSO_4$). The solvent was removed and the residue was purified by column chromatography on silica gel

(eluting with dichloromethane-methanol gradient) to give the title compound (D2) as a tan gum (0.21g, 60%). MS: m/z (MH+) = 352.

Description 3

2-(2-Methoxy-5-nitrophenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D3)

A mixture of {2-[(2-methoxy-5-nitrophenylamino)methyl]piperidin-1-yl}acetic acid ethyl ester (D2) (0.3 g, 0.85 mmol) and sodium metal (20 mg, 0.87 mmol) in dry dioxane (8 mL) was heated under reflux for 40 minutes. The mixture was concentrated to a small volume, diluted with dichloromethane (50 mL), washed with brine (2 x 10 mL) and dried ($MgSO_4$). The solvents were removed and the residue was purified by column chromatography on silica gel (eluting with dichloromethane-ethyl acetate gradient) to give the required product (D3) as a tan oil (0.08 g, 31%). MS: m/z (MH+) = 306.

Description 4

2-(5-Amino-2-methoxyphenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D4)

2-(2-Methoxy-5-nitrophenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D3) (0.04 g) and Pd/C (0.05 g) in ethanol (15 mL) were stirred at room temperature under atmosphere of hydrogen for 4 hours. The catalyst was filtered off and washed with ethanol (2 x 15 mL). The filtrate and washings were combined and evaporated to dryness. The residue was co-evaporated with dry toluene (2 x 10 mL) to give the title compound (D4) as a colourless gum (0.035 g, 97%). MS: m/z (MH+) = 276.

Description 5

4-Methoxy-3-(octahydropyrido[1,2-*a*]pyrazin-2-yl)phenylamine (D5)

A solution of 2-(5-amino-2-methoxyphenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D4) (0.035 g, 0.13 mmol) and borane-THF complex (1M solution, 1 mL) in tetrahydrofuran (5 mL) was heated under reflux for 4 hours. Dry methanol (2 mL) was added and the solvents were removed. The residue was redissolved in dry methanol (5 mL) and cesium fluoride (0.035 g, 0.23 mmol)) and dry potassium carbonate (0.035 g, 0.25 mmol) were added. The mixture was then heated under reflux for 5 hours. The solvent was removed, the residue was partially dissolved in dichloromethane (30 mL), washed with brine (3 x 10 mL), water (1 x 10 mL) and dried ($MgSO_4$). The solvent was removed to give the required product (D5) as a slightly tan glass (0.03g, 90%). MS: m/z (MH+) = 262.

Description 6

[N-(*tert*-Butoxycarbonyl)-L-prolinyl]-2-methoxy-5-nitrobenzeneamide (D6)

Ethyl chloroformate (1.3 mL, 14 mmol) was added dropwise to a solution of N-(*tert*-butoxycarbonyl)-L-proline (3.0 g, 14 mmol) and 4-methylmorpholine (1.54 mL, 14 mmol) in tetrahydrofuran (30 mL) at - 10 °C. The resulting mixture was stirred at - 10 °C for 10 minutes and 2-methoxy-5-nitroaniline (2.35g, 14 mmol) was added. The mixture was stirred at -10°C for 30 minutes and then at room temperature for 17 hours. The precipitate was removed by fitration and washed with tetrahydrofuran (3 x 20 mL). The filtrate and washings were combined and evaporated to dryness. The residue was dissolved in dichloromethane (100 mL), washed with aqueous sodium hydrogen carbonate (2 x 30 mL), dried (Na_2SO_4). The solvent was removed and the product was purified by column chromatography on silica gel (eluting with dichloromethane-ethyl acetate gradient) to give the title amide (D6) as a colourless glass (3.81 g, 75%). MS: m/z (MHNa+) =389.

Description 7

S-Pyrrolidine-2-carboxylic acid (2-methoxy-5-nitrophenyl)amide (D7)

A solution of [N-(*tert*-butoxycarbonyl)-L-prolinyl]-2-methoxy-5-nitrobenzene-amide (D6) (1.8g, 4.93 mmol), trifluoroacetic acid (2.65 mL) and water (0.1 ml) in dichloromethane (15 mL) was stirred at room temperature for 17 hours. The solvents were removed and the residue was co-evaporated with toluene (2 x 40 mL). The resulting solid was dissolved in dichloromethane (200 mL) and washed with aqueous sodium hydrogen carbonate (2 x 50 mL). The aqueous layer was extracted with dichloromethane (4 x 50 mL), the combined extracts were dried (Na_2SO_4) and finally the solvent was removed to give the title compound (D7) as a cream solid (1.01 g, 77%). MS: m/z (MH+) = 266.

Description 8

S-1-Bromoacetylpyrrolidine-2-carboxylic acid (2-methoxy-5-nitro-phenyl)-amide (D8)

To a solution of S-pyrrolidine-2-carboxylic acid (2-methoxy-5-nitro-phenyl)-amide (D7) (0.2 g, 0.75 mmol) and N,N-diisopropylethylamine (0.13 mL, 0.75 mmol) in dichloromethane (10 mL) at -10°C was added dropwise bromoacetyl bromide (0.75 mmol, 0.07 mL) in dichloromethane (1 mL). The resulting reaction mixture was stirred at -10°C for 30 minutes and then at room temperature for 20 minutes. Subsequently, it was diluted with dichloromethane (50 mL), washed with aqueous sodium hydrogen carbonate (1 x 20 mL), water (1 x 20 mL) and dried (Na_2SO_4). The solvent was removed and the residue was co-evaporated with toluene (2 x 20 mL) to give the product (D8) (0.29 g) which was used without purification in the next step. MS: m/z (MH+) = 387.

Description 9

S-2-(2-Methoxy-5-nitrophenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D9)

A mixture of S-1-bromoacetylpyrrolidine-2-carboxylic acid (2-methoxy-5-nitrophenyl)amide (D8) (0.28 g, 0.7 mmol) and NaH (50 mg, 60% dispersion in mineral oil) in N,N-dimethylformamide (5 mL) was stirred at room temperature for 2 hours. A further amount of NaH was then added and the mixture was stirred at room temperature for additional 17 hours. The precipitate was filtered off and washed with dichloromethane (60 mL). The filtrate and washings were combined and evaporated to dryness. The residue was co-evaporated with toluene (2 x 10 mL). The product was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (D9) as a colourless solid (0.079 g, 34% after two steps). MS: m/z (MH+) = 306.

Description 10

S-2-(5-Amino-2-methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D10)

A mixture of S-2-(2-methoxy-5-nitrophenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D9) (0.07 g) and Pd/C (0.08 g) in ethanol-ethyl acetate (8:2, 40 mL) was stirred at room temperature under atmosphere of hydrogen for 7.5 hours. The catalyst was filtered off, washed with ethanol (3 x 15 mL) and ethyl acetate (1 x 15 mL). The filtrate and washings were combined and evaporated to dryness. The product was purified by column chromatography (eluting with dichloromethane-methanol gradient) to give the title compound (D10) as a colourless solid (0.056 g, 89%). MS: m/z (MH+) = 276.

Description 11

S-3-(Hexahydropyrrolo[1,2-*a*]pyrazine-2-yl)-4-methoxyphenylamine (D11)

A solution of S-2-(5-amino-2-methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D10) (0.055 g, 0.2 mmol) and borane-THF complex (1M solution, 1.2 mL) in tetrahydrofuran (5 mL) was heated under reflux for 5 hours. A further amount of borane-THF complex (1M solution, 0.6 mL) was then added and the reaction was heated under reflux for another 2 hours. The solution was diluted with dry methanol (5 mL) and the solvents were removed. The residue was co-evaporated with dry benzene (2 x 5 mL) and redissolved in dry methanol (5 mL). Cesium fluoride (0.8 mmol, 0.12g) and dry potassium carbonate (0.87 mmol, 0.12 g) were added to the solution and the mixture was heated under reflux for 17 hours. A further amount of methanol (5 mL), cesium fluoride (0.8 mmol, 0.12g) and dry potassium carbonate

(0.87 mmol, 0.12 g) was then added and the reflux was continued for another 6 hours. Cesium fluoride (0.4 mmol, 0.06 g) and dry potassium carbonate (0.43 mmol, 0.06 g) were added again and the reflux was continued for 3 hours. The solvent was removed, the residue was partially dissolved in dichloromethane (50 mL), washed with brine (3 x 20 mL), water (1 x 10 mL) and dried (Na_2SO_4). The solvent was removed to give the title compound (D11) as a tan gum (0.042 g, 85%). MS: m/z (MH+) = 248.

Description 12

2-(2-Methoxyphenyl)-5-methyl-*cis*-octahydropyrrolo[3,4-c]pyrrole (D12)

A suspension of cesium carbonate (15g, 46mmol), palladium (II) acetate (0.15g, 0.7mmol) and 2,2'-bis(diphenylphosphine)-1,1'-binaphthyl (0.63g, 1mmol) in dry 1,4-dioxan (50ml) was degassed, purged with argon and sonicated for 10 minutes. 2-Bromoanisole (3.3ml, 27mmol) and *cis*-hexahydro-2-methylpyrrolo[3,4-c]pyrrole hydrochloride [US 5,457,121 (1995)](1.9g) were added and the whole was again degassed, purged with argon and sonicated for 10 minutes. The stirred mixture was then refluxed under argon for 20 hours. The mixture was partitioned between dichloromethane (200ml) and 1M sodium hydroxide solution (100ml). The aqueous layer was further extracted with dichloromethane (50ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to an oil. The oil was purified by column chromatography on silica gel eluting with a gradient of dichloromethane/methanol to afford the title compound (D12) as a solid (1.2g, 56%). ^{1}H NMR ($CDCl_3$, 250MHz) 2.34 (3H, s), 2.43-2.48 (2H, m), 2.62-2.69 (2H, m), 2.85-2.92 (2H, m), 2.99-3.04 (2H, m), 3.34-3.41 (2H, m), 3.85 (3H, s), 6.80-6.94 (4H, m); (MH+) 232.

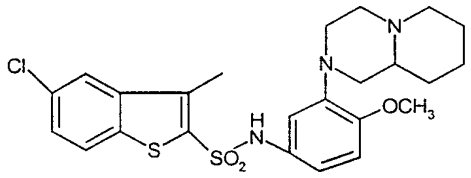
Description 13

4-Methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-benzenesulfonyl chloride (D13)

A solution of 2-(2-methoxyphenyl)-5-methyl-*cis*-octahydropyrrolo[3,4-c]pyrrole (D12) (0.5g, 2.2mmol) in dry dichloromethane (3ml) was added over 5 minutes to ice cooled chorosulfonic acid (3ml) under argon. After stirring at 0°C for 0.25 hours and subsequently at room temperature for 1 hour, the solution was slowly poured onto a stirred mixture of ice (50g) and dichloromethane (50ml). The mixture was basified by addition of excess saturated solution of sodium carbonate and the layers were separated. The aqueous layer was further extracted with dichloromethane (50ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (D13) as a foam (0.25g 34%).

Example 1

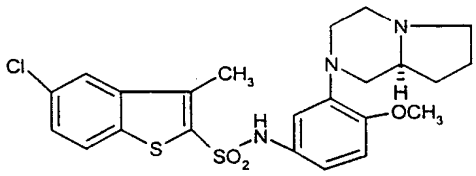
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[4-methoxy-3-(octahydropyrido[1,2-α]pyrazin-2-yl) phenyl] amide (E1)



A solution of 4-methoxy-3-(octahydropyrido[1,2-α]pyrazin-2-yl)phenylamine (D5) (0.03 g, 0.11 mmol), 5-chloro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.042 g, 0.15 mmol) and triethylamine (0.02mL, 0.15 mmol) in dichloromethane (2 mL) was stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane (20 mL), washed with saturated aqueous sodium hydrogen carbonate ((1 x 10 mL) and dried ($MgSO_4$). The solvent was removed and the product was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (E1) as a cream solid (0.019 g, 32%). δ_H (250MHz, $CDCl_3$), 1.28 (3H, m), 1.73 (3H, m), 2.08 (3H, m), 2.19 (3H, s), 2.43 (1H, m), 2.68 (1H, m), 2.84 (2H, m), 3.00 (1H, m), 3.21(1H, m), 3.82 (3H, s), 6.46 (1H, d, J = 2.34 Hz), 6.73 (2H, m), 7.42 (1H, m), 7.65 (1H, d, J = 1.91 Hz), 7.72 (1H, d, J = 8.62 Hz). MS: m/z (MH+) = 506.

Example 2

S-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2-α]pyrazine-2-yl)-4-methoxyphenyl]amide (E2)



A solution of S-3-(hexahydropyrrolo[1,2-α]pyrazine-2-yl)-4-methoxy-phenylamine (D11) (0.04 g, 0.16 mmol), 5-chloro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.045 g, 0.16 mmol) and pyridine (0.1 mL, 1.2 mmol) in dichloromethane (4 mL) was stirred at room temperature for 2 days. The mixture was diluted with dichloromethane (30 mL), washed with saturated aqueous sodium hydrogen carbonate (2 x 10 mL) and dried (Na_2SO_4). The solvent was removed and the product was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (E2) as a pink glass (0.047 mg, 59%).

δ_H (250MHz, $CDCl_3$), 1.31 (1H, m), 1.82 (3H, m), 2.10 (3H, m), 2.22 (3H, s), 2.41 (1H, m), 2.60 (1H, m), 3.02 (1H, m), 3.17 (3H, m), 3.81 (3H, s), 6.51 (1H, d, J = 2.08 Hz), 6.70 (2H, m), 7.43 (1H, m), 7.66 (1H, d, J = 1.90 Hz), 7.74 (1H, d, J = 8.60 Hz). MS: m/z (MH+) = 492.

Example 3

R-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2-α]pyrazine-2-yl)-4-methoxyphenyl]amide (E2)

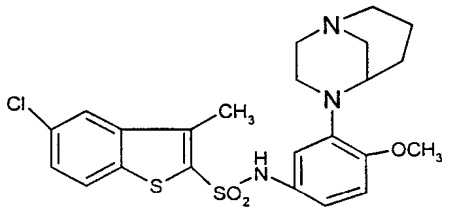
Following the same procedures as described for Example 2 the title compound (E3) was prepared from N-(*tert*-butoxycarbonyl)-D-proline; 28% yield;

δ_H (250MHz, $CDCl_3$), 1.30 (1H, m), 1.81 (3H, m), 2.11 (3H, m), 2.22 (3H, s), 2.38 (1H, m), 2.60 (1H, m), 3.01 (1H, m), 3.18 (3H, m), 3.80 (3H, s), 6.50 (1H, d, J = 2.16 Hz), 6.70 (2H, m), 7.44 (1H, m), 7.66 (1H, d, J = 1.90 Hz), 7.74 (1H, d, J = 8.60 Hz). MS: m/z (MH+) = 492.

The following examples may be prepared by similar procedures to those described for Examples 1 and 2.

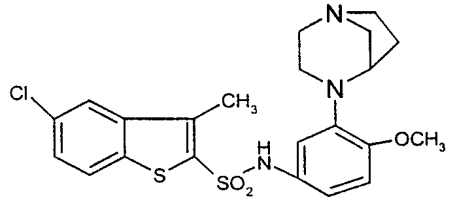
Example 4

5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[3-(1,4-diazabicyclo-[3.3.1]non-4-yl)-4-methoxyphenyl]amide (E4)



Example 5

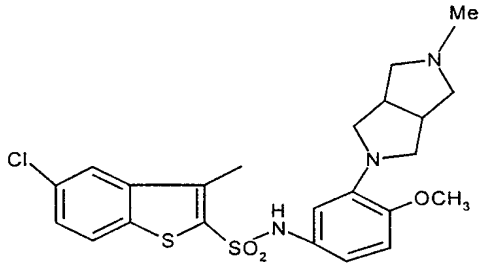
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(1,4-diazabicyclo-[3.2.1]oct-4-yl)-4-methoxyphenyl]amide (E5)



The following examples may be prepared by similar procedures to those described for Example 1 employing the methodology described in US-5457121.

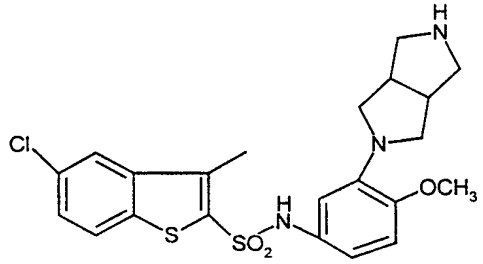
Example 6

5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [4-methoxy-3-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)phenyl]amide (E6)



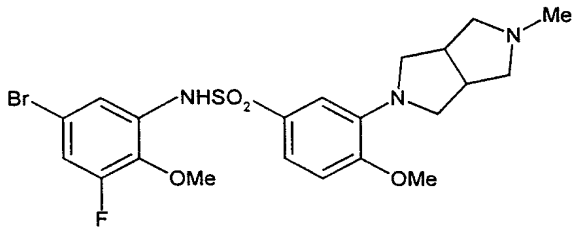
Example 7

5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydropyrrolo-[3,4-*c*]pyrrol-2-yl)-4-methoxyphenyl]amide (E7)



Example 8

N-(5-Bromo-3-fluoro-2-methoxyphenyl)-4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-c]pyrrol-2-yl]-benzenesulfonamide hydrochloride (E8)



A solution of 5-bromo-3-fluoro-2-methoxy-aniline (160mg, 0.73mmol) and 4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-benzenesulfonyl chloride (D13) (240mg, 0.73mmol) in dichloromethane (4ml) was stirred for 18 hours under argon. The solution was concentrated *in vacuo* and the residue was purified by

column chromatography eluting with a dichloromethane/methanol gradient to give the title compound (**E8**) as a foam (95mg, 24%); (MH+) 514/516.

Method for assay of 5-HT6 antagonistic activity:

The test compounds were dissolved in polyethylene glycol:dimethyl sulphoxide (1:1) at 1 or 10mM and diluted to 0.1mM using 5mM tris buffer (pH 7.7 @ 25°C). Dissolution was assisted by addition of 0.02ml 5M HCl plus heating to 40°C and sonication for 10 minutes. Serial dilutions of test compounds in the same buffer were carried out using either a TECAN 5052 or Biomek 2000 Workstation. Samples of the diluted test compounds (0.05ml) were mixed with 0.05ml of radio-ligand [^{3}H]-LSD prepared in the incubation buffer, and 0.4ml of a suspension of a preparation of the washed membranes of HeLa_5HT6 cells (acquired from Dr. D. Sibley, NIH, Bethesda, see Ref 1)(see Table 1), also in the incubation buffer. The details of the incubation conditions for each assay are shown in Table 2. The incubation buffer was 50mM Trizma (Sigma, UK) pH7.7 @ 25°C, 4mM $MgCl_2$.

After incubation at 37°C, the mixtures were filtered using a Packard Filtermate in Packard TopCount format. Filters were washed with 4 x 1ml aliquots of ice-cold incubation buffer. Filters were dried and impregnated with 0.04ml of Microscint 20 (Packard). IC_{50} values were estimated from the counts per minute using a four parameter logistic curve fit within EXCEL (2). K_i values were calculated using the method of Cheng and Prusoff (3). pIC_{50} and pK_i are the negative log10 of the molar IC_{50} and K_i respectively.

Table 1 Details of the methods used to prepare membranes for binding assays

1st resuspension cells/ml	spin / resuspension 1, 2 ,3	Incubation before final spin	protein conc. in stored aliquots	cells /ml in stored aliquots
7×10^7	Yes	20min at 37°C	4mg/ml	1.0×10^8

Table 2 Summary of receptor binding assay conditions

protein (ug/ sample)	radio-ligand [^{3}H]-LSD (nM)	Specific Activity (Ci/mmol)	Non-Specific Definition	Kd (nM)
40	2.0	83	Methiothepin	3.1

References

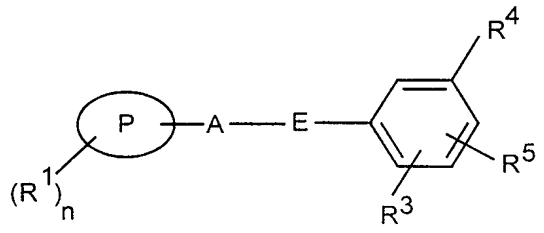
1. MONSMA, F.J., SHEN, Y., WARD, R.P., HAMBLIN, M.W., SIBLEY, D.R.. 1993. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.*, **43,** 320-327.

2. BOWEN, W.P., JERMAN, J.C.. 1995. Nonlinear regression using spreadsheets. *Trends in Pharmacol. Sci.*, **16,** 413-417.

3. CHENG, Y.C., PRUSSOF, W.H.. 1973. Relationship between inhibition constant (Ki) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.*, **92,** 881-894.

Claims:

1 A compound of formula (I) or a salt thereof:



(I)

in which

E is $-SO_2NH-$ or $-NHSO_2^-$

P is a phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6}alkylene or a C_{1-6}alkenylene group;

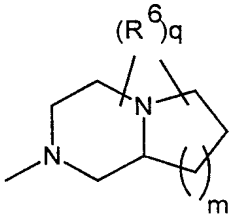
R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more fluorine atoms, C_{3-6}cycloalkyl, C_{1-6}alkoxy, OCF_3, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, amino, alkylamino or dialkylamino, SR^{11} where R^{11} is hydrogen or C_{1-6}alkyl or R^1 is phenyl, benzyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; and

n is 0, 1, 2, 3, 4 or 5;

R^3 is a group R^5 or together with R^5 forms a group $(CH_2)_2O$ or $(CH_2)_3O$;

R^4 is selected from a group of formula (i), (ii) or (iii)

Formula (i)

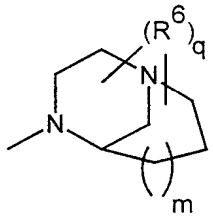


in which R^6 is C_{1-6}alkyl optionally substituted by one or more halogen atoms;

m is 0, 1 or 2;

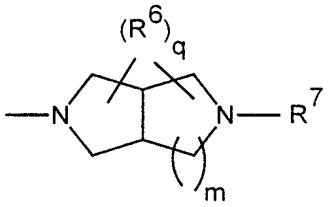
q is 0, 1, 2, 3 or 4; or

Formula (ii)



in which R^6, m and q are as defined in formula (i); or

Formula (iii)



in which R^6, m and q are as defined in formula (I) and R^7 is hydrogen or C_{1-6}alkyl; R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy optionally substituted with one or more fluorine atoms, trifluoromethyl, or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$.

2. A compound according to claim 1 in which P is phenyl or benzothienyl.

3. A compound according to claims 1 and 2 in which A is a single bond.

4. A compound according to any one of claims 1 to 3 in which R^3 is hydrogen.

5. A compound according to any one of claims 1 to 4 in which R^5 is C_{1-6}alkoxy.

6. A compound according to any one of claims 1 to 5 in which R^5 is para with respect to the sulphonamide linkage.

7. A compound according to claim 1 which is:
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[4-methoxy-3-(octahydropyrido[1,2-α]pyrazin-2-yl) phenyl] amide,
S-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2-α]pyrazine-2-yl)-4-methoxyphenyl],

R-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2-α]pyrazine-2-yl)-4-methoxyphenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[3-(1,4-diazabicyclo-[3.3.1]non-4-yl)-4-methoxyphenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(1,4-diazabicyclo-[3.2.1]oct-4-yl)-4-methoxyphenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [4-methoxy-3-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)phenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydropyrrolo-[3,4-*c*]pyrrol-2-yl)-4-methoxyphenyl]amide,
N-(5-Bromo-3-fluoro-2-methoxyphenyl)-4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-c]pyrrol-2-yl]-benzenesulfonamide
and pharmaceutically acceptable salts thereof.

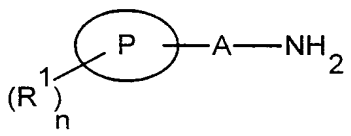
8. A compound according to any one of claims 1 to 7 for use in therapy.

9. A compound according to any one of claims 1 to 7 for use in the treatment of cognitive memory disorders, Parkinson's Disease, schizophrenia and/or depression.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

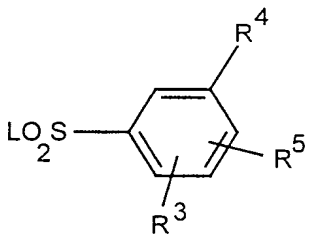
11. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) when E is a group $-NHSO_2^-$, the coupling of a compound of formula (II):



(II)

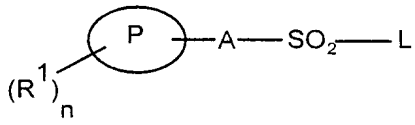
in which R^1, P, n and A or protected derivatives thereof with a compound of formula (III):



(III)

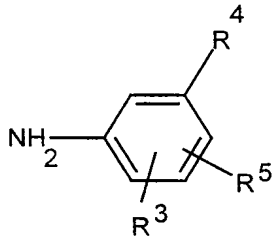
in which R^3, R^4 and R^5 are as defined in formula (I) and L is a leaving group; or

(b) when E is a group $-SO_2NH-$, the coupling of a compound of formula (IV):



(IV)

in which R^1, P, n and A are defined in formula (I) and L is a leaving group with a compound of formula (V) or protected derivatives thereof:



(V)

in which R^3, R^4 and R^5 are as defined for formula (I)

and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.